














Affiliated Pharmarisk Cardiac Created for:

Patient:
HIPAA Compliant Fax:
Physician:
Address:
Collection Date:
Specimen Type:

Accession #:
Gender:
DOB:
Received Date:
Report Generated:

Key Test Findings

Pharmacogenetic Results				
Assay	Results	Phenotype	Clinical Consequences	
 ANKK1/DRD2	DRD2:Ta1A AG	Altered DRD2 function	Consistent with a reduced dopamine receptor D2 function.	
 COMT	Val158Met GG	High COMT Activity	Consistent with a normal catechol O-methyltransferase (COMT) function.	
 CYP1A2	*1F/*1F	Normal Metabolizer - Higher Inducibility	Consistent with a typical CYP1A2 activity in absence of inducing substances. Rapid Metabolism occurs in presence of inducers such as barbiturates, cruciferous vegetables, carbamazepine, rifampin and smoking.	
 CYP2B6	*1/*1	Normal Metabolizer	Consistent with a typical CYP2B6 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates.	
 CYP2C19	*2/*17	Intermediate Metabolizer	Consistent with a moderate deficiency in CYP2C19 activity. Potential risk for side effects or loss of efficacy with drug substrates.	
 CYP2C9	*1/*1	Normal Metabolizer	Consistent with a typical CYP2C9 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates.	
 CYP2D6	*2/*4/*5	Poor Metabolizer	Consistent with a significant deficiency in CYP2D6 activity. Increased risk for side effects or loss of efficacy with drug substrates.	
 CYP3A4	*1/*1B	Normal Metabolizer	Consistent with a typical CYP3A4 activity. Caution is advised when prescribing narrow therapeutic index drugs. Alternative drugs or dose adjustment may be required if CYP3A inhibitors or inducers are co-prescribed.	
 CYP3A5	*1/*3	Intermediate Metabolizer	Consistent with an intermediate CYP3A5 activity. Caution is advised when prescribing narrow therapeutic index drugs. Alternative drugs or dose adjustment may be required if CYP3A inhibitors or inducers are co-prescribed.	
 OPRM1	A118G AA	Normal OPRM1 Function	Consistent with a good analgesia at standard opioid doses. Consistent with a poor response to naltrexone.	
 SLCO1B1	521T>C TT	Normal Transporter Function	Consistent with a typical SLCO1B1 transporter function. The patient's risk for statin-induced myopathy is not increased.	
 UGT2B15	*2/*2	Poor Metabolizer	Consistent with a decreased UGT2B15 glucuronidation function. Potential risk for side effects with drug substrates.	
 VKORC1	-1639G>A G/G	Low Warfarin Sensitivity	VKORC1 is the site of action of warfarin. The patient may require an increase in warfarin dose.	

Cardiovascular/Thrombosis Risk Management				
	Gene	Genotype	Phenotype	Clinical Consequences
✓	Factor II Factor V Leiden	20210G>A GG 1691G>A GG	No Increased Risk of Thrombosis	Unless other genetic or circumstantial risk factors are present, the patient is not expected to have an increased risk for thrombosis.
✓	MTHFR MTHFR	1298A>C AC 677C>T CC	No Increased Risk of Hyperhomocysteinemia.	The patient MTHFR function is slightly reduced and no significant hyperhomocysteinemia is expected.
✓	Apolipoprotein E	ε3/ε3	No Increased Risk of Hyperlipidemia/Atherosclerotic Vascular Disease	The patient has a normal APOE genotype and unless other genetic or circumstantial risk factors are present, his risk for hyperlipidemia/atherosclerotic vascular disease is not increased.

Cardiovascular/Thrombosis Risk Management

- ✓ **Thrombophilia**
No Increased Risk of Thrombosis
Unless other genetic and/or circumstantial risk factors are present (ex: smoking, obesity...), estrogen-containing contraceptive and hormone replacement therapy can be used by the patient.
- ✓ **Hyperhomocysteinemia**
No Increased Risk of Hyperhomocysteinemia
The patient sensitivity to methotrexate is not increased.
- ✓ **Hyperlipidemia/Atherosclerotic Vascular Disease**
No increased risk of hyperlipidemia/atherosclerotic vascular disease
No action is needed when a patient in normolipidemic.

Medication Guidance

Psychotropic Medications		
Standard Precautions	Use With Caution	Consider Alternatives
Amphetamine (Adderall) Citalopram (Celexa) Desvenlafaxine (Pristiq) Dexmethylphenidate (Focalin) Dextroamphetamine (Dexedrine) Diazepam (Valium) Escitalopram (Lexapro) Lisdexamfetamine (Vyvanse) Methylphenidate (Ritalin) Mirtazapine (Remeron) Paliperidone (Invega) Phenytoin (Dilantin)	Aripiprazole (Abilify) Atomoxetine (Strattera) Bupropion (Wellbutrin) Clobazam (Onfi) Clozapine (Clozaril) Donepezil (Aricept) Duloxetine (Cymbalta) Galantamine (Razadyne) Iloperidone (Fanapt) Lorazepam Naltrexone (Vivitrol) Olanzapine (Zyprexa) Oxazepam Paroxetine (Paxil) Perphenazine (Trilafon) Pimozide (Orap) Sertraline (Zoloft) Tetrabenazine (Xenazine)	Amitriptyline (Elavil) Clomipramine (Anafranil) Desipramine (Norpramin) Doxepin (Silenor) Haloperidol (Haldol) Imipramine (Tofranil) Nortriptyline (Pamelor) Risperidone (Risperdal) Thioridazine (Mellaril) Trimipramine (Surmontil) Venlafaxine (Effexor)
Cardiovascular Medications		
Standard Precautions	Use With Caution	Consider Alternatives
Atorvastatin (Lipitor) Fluvastatin (Lescol) Irbesartan (Avapro) Lovastatin (Mevacor) Nebivolol (Bystolic) Pitavastatin (Livalo) Prasugrel (Effient) Pravastatin (Pravachol) Propranolol (Inderal) Rosuvastatin (Crestor) Simvastatin (Zocor) Ticagrelor (Brilinta) Warfarin (Coumadin)	Carvedilol (Coreg) Flecainide (Tambocor) Mexiletine (Mexitil) Propafenone (Rythmol) Timolol (Timoptic)	Clopidogrel (Plavix) Metoprolol (Lopressor)
Pain Medications		
Standard Precautions	Use With Caution	Consider Alternatives
Carisoprodol (Soma) Celecoxib (Celebrex) Fentanyl (Actiq) Flurbiprofen (Ansaid) Hydrocodone (Vicodin) Methadone (Dolophine) Oxycodone (Percocet) Piroxicam (Feldene)	Morphine (MS Contin) Tizanidine (Zanaflex)	Codeine (Codeine) Tramadol (Ultram)

Other Medications		
Standard Precautions	Use With Caution	Consider Alternatives
Dexlansoprazole (Dexilant)	Darifenacin (Enablex)	
Esomeprazole (Nexium)	Tacrolimus (Prograf)	
Fesoterodine (Toviaz)	Tamsulosin (Flomax)	
Glimepiride (Amaryl)	Tolterodine (Detrol)	
Glipizide (Glucotrol)		
Glyburide (Micronase)		
Lansoprazole (Prevacid)		
Omeprazole (Prilosec)		
Ondansetron (Zofran)		
Pantoprazole (Protonix)		
Rabeprazole (Aciphex)		
Tolbutamide (Orinase)		
Voriconazole (Vfend)		

Test Details

Gene	Alleles Tested
ANKK1/DRD2	DRD2:Taq1A
Apolipoprotein E	ε2, ε4
COMT	Val158Met
CYP1A2	*1C, *1D, *1F, *1K, *1L, *1V
CYP2B6	*4, *5, *11, *9, *6, *8, *18, *22, *28
CYP2C19	*2, *3, *4, *4B, *5, *6, *7, *8, *9, *10, *12, *17
CYP2C9	*2, *3, *4, *5, *6, *8, *10, *11, *25
CYP2D6	*2, *11, *15, *3, *4, *4M, *6, *7, *8, *10, *12, *14A, *17, *18, *19, *20, *38, *29, *35, *44, *41, *56, *5 (gene deletion), XN (gene duplication)
CYP3A4	*22, *1B, *2, *3, *12, *17
CYP3A5	*1D, *2, *3, *3C, *5, *6, *7, *8, *9
Factor II	20210G>A
Factor V Leiden	1691G>A
MTHFR	1298A>C
MTHFR	677C>T
OPRM1	A118G
SLCO1B1	*5, *15
UGT2B15	*2
VKORC1	1542G>C, -1639G>A, 1173C>T

Methodology:

Testing is performed on DNA extracted from a buccal swab. Samples are genotyped using Taqman® allele discrimination assays. The assays detect alleles listed above, including all common and most rare variants with known clinical significance at analytical sensitivity and specificity >99%.

Limitations:

The interpretations provided in this report are provided to assist health care providers, but they are not a treatment recommendation. Diagnosis and treatment remain the sole responsibility of the ordering physician. While the polymorphisms tested are important, other variants and mutations in these genes will not be detected. Mutations in other genes that could affect drug metabolism will not be detected. Non-genetic factors also affect metabolism. This test is not a substitute for clinical and therapeutic drug monitoring. This report does not address patient drug allergies or drug-drug interactions.

Signature:


Kenneth Ward M.D.

Date: 1/29/2014

CLIA FDA Statement:

This Laboratory Developed Test was developed and its performance characteristics determined by Affiliated Genetic, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing and has established and verified the test's accuracy. This test has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. These results are adjunctive to an ordering physician's diagnosis.

Appendix: Dosing Guidance

Amitriptyline (Elavil)

Increased Sensitivity to Amitriptyline (CYP2D6 *2/*4/*5 Poor Metabolizer)

Select an alternative drug or consider prescribing amitriptyline at a reduced dose (50% reduction) with monitoring of plasma concentrations of amitriptyline and nortriptyline. Available alternative drugs not sensitive to CYP2D6 function include: sertraline, citalopram, escitalopram and fluvoxamine.

Aripiprazole (Abilify)

Increased Sensitivity to Aripiprazole (CYP2D6 *2/*4/*5 Poor Metabolizer)

Aripiprazole dose should initially be reduced to one-half (50%) of the usual dose and then adjusted to achieve a favorable clinical response. Reduce the maximum dose to 10 mg/day (67% of the maximum recommended daily dose). The dose of aripiprazole for poor metabolizers patients who are administered a strong CYP3A4 inhibitor should be reduced to one-quarter (25%) of the usual dose.

Atomoxetine (Strattera)

Increased Sensitivity to Atomoxetine (CYP2D6 *2/*4/*5 Poor Metabolizer)

Careful titration is recommended with monitoring for toxicity until a favorable response is achieved. In children and adolescents up to 70 kg body weight, atomoxetine should be initiated at standard dosing of 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated. In children and adolescents over 70 kg body weight and adults, atomoxetine should be initiated at standard dosing of 40 mg/day and only increased to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

Bupropion (Wellbutrin)

Decreased Response to Bupropion (ANKK1 DRD2:Taq1A AG Altered DRD2 function)

Smoking Cessation: The patient's genotype is associated with a positive response to nicotine replacement therapy and a lesser response to bupropion treatment.

Carvedilol (Coreg)

Moderate Sensitivity to Carvedilol (CYP2D6 *2/*4/*5 Poor Metabolizer)

Carvedilol can be prescribed at standard label recommended-dosage and administration. CYP2D6 poor metabolizers may experience dizziness during up-titration. Careful titration is recommended with monitoring until a favorable response is achieved.

Clobazam (Onfi)

Possible Sensitivity to Clobazam (CYP2C19 *2/*17 Provisional Intermediate Metabolizer)

In CYP2C19 Intermediate metabolizers, plasma levels of the active metabolite N-desmethyloclobazam were 2-fold higher than those found in CYP2C19 normal metabolizers. The dose adjustment for intermediate metabolizers is not well established; therefore, the recommendation for poor metabolizers is proposed. The starting dose should be 5 mg/day and dose titration should proceed slowly according to weight. Patients should be titrated initially to 10 mg /day (≤ 30 kg body weight) or 20 mg/day (>30 kg body weight). If necessary and based upon clinical response, an additional titration to the maximum doses 20 mg/day (≤ 30 kg body weight) or 40 mg/day (>30 kg body weight) may be started on day 21.

Clomipramine (Anafranil)

Increased Sensitivity to Clomipramine (CYP2D6 *2/*4/*5 Poor Metabolizer)

Consider alternative or prescribe clomipramine at 50% of recommended standard starting dose. Monitor plasma concentrations of clomipramine and desmethyloclobazam and titrate accordingly until a favorable response is achieved.

Clopidogrel (Plavix)

Reduced Response to Clopidogrel (CYP2C19 *2/*17 Provisional Intermediate Metabolizer)

Consider alternative therapy. Example of alternative drugs: Prasugrel (contraindicated in TIA/Stroke patients); Ticagrelor; Aspirin; Aspirin plus Dipyridamole.

Clozapine (Clozaril)

Non-Response to Clozapine (CYP1A2 *1F/*1F Normal Metabolizer - Higher Inducibility)

Smokers have a high risk for non-response and may require higher doses. There is an association between high clozapine doses and the risk of seizures, therefore careful monitoring is recommended during dosing adjustment. Smoking cessation will increase plasma drug levels leading to adverse events and therapeutic drug monitoring accompanied by dose reduction is recommended in patients who have quit smoking.

Codeine (Codeine)

Non-Response to Codeine (CYP2D6 *2/*4/*5 Poor Metabolizer)

Avoid prescribing codeine and consider alternative opioids other than tramadol or consider a non-opioid analgesic such as a NSAID or a COX-2 inhibitor. Unless contraindicated, available alternative opioids (not sensitive to CYP2D6 function) include: Fentanyl, Morphine, Hydromorphone, Oxymorphone, Tapentadol and Meperidine.

Darifenacin (Enablex)

Possible Sensitivity to Darifenacin (CYP2D6 *2/*4/*5 Poor Metabolizer)

Darifenacin exposure is increased 30% in CYP2D6 poor metabolizers. Although no dose adjustment may not be needed in these patients, monitor patients for increased side effects when darifenacin is prescribed at standard label recommended-dosage and administration.

Desipramine (Norpramin)

Increased Sensitivity to Desipramine (CYP2D6 *2/*4/*5 Poor Metabolizer)

Consider alternative or prescribe desipramine at 50% of recommended standard starting dose. Monitor plasma concentrations of desipramine and metabolites and titrate accordingly until a favorable response is achieved.

Donepezil (Aricept)

Possible Altered Response to Donepezil (CYP2D6 *2/*4/*5 Poor Metabolizer)

When compared to a normal metabolizer, a poor metabolizers has a 30% decrease in donepezil clearance; the clinical significance of this decrease is not well documented. Consider using a standard dosing regimen and be alert for adverse events and adjust dosage in response to clinical response and tolerability.

Doxepin (Silenor)

Increased Sensitivity to Doxepin (CYP2D6 *2/*4/*5 Poor Metabolizer)

Consider alternative drug or reduce doxepin starting dose by 50%. Adjust maintenance dose according to nordoxepin plasma concentrations. Available alternative drugs not sensitive to CYP2D6 function include: sertraline, citalopram, escitalopram and fluvoxamine.

Duloxetine (Cymbalta)

Possible Sensitivity to Duloxetine (CYP2D6 *2/*4/*5 Poor Metabolizer)

Limited data suggest that duloxetine plasma concentrations might be increased in poor metabolizers of CYP2D6, therefore duloxetine can be prescribed at standard label recommended-dosage and careful titration is recommended until a favorable response is achieved.

Flecainide (Tambocor)

Significantly Increased Sensitivity to Flecainide (CYP2D6 *2/*4/*5 Poor Metabolizer)

Consider prescribing a lower flecainide dose. When compared to a CYP2D6 normal metabolizer, a poor metabolizer may require a 50% dose reduction. Careful titration with ECG recording and monitoring of flecainide plasma concentrations are recommended until a favorable clinical response is achieved.

Galantamine (Razadyne)

Possible Sensitivity to Galantamine (CYP2D6 *2/*4/*5 Poor Metabolizer)

A CYP2D6 poor metabolizer has a drug exposure that is approximately 50% higher than the exposure in a normal metabolizer. Although, dosage adjustment is not necessary in a patient identified as a CYP2D6 poor metabolizer as the dose of drug is individually titrated to tolerability, a slower titration can be considered as it may improve tolerability.

Haloperidol (Haldol)

Increased Sensitivity to Haloperidol (CYP2D6 *2/*4/*5 Poor Metabolizer)

Consider alternative drug or prescribe haloperidol at 50% of the usual starting dose and then adjust dosage to achieve a favorable clinical response. Be alert to increased haloperidol plasma concentrations. Available alternative drugs include: pimozide; fluphenazine, quetiapine, olanzapine and clozapine.

Iloperidone (Fanapt)

Increased Sensitivity to Iloperidone (CYP2D6 *2/*4/*5 Poor Metabolizer)

Iloperidone **dose should be reduced by one-half and titrate slowly to avoid orthostatic hypotension**. Because iloperidone is associated with QTc prolongation, caution is warranted when prescribing the drug in patients with reduced CYP2D6 activity. If patients taking iloperidone experience symptoms that could indicate the occurrence of cardiac arrhythmias, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, including cardiac monitoring.

Imipramine (Tofranil)

Increased Sensitivity to Imipramine (CYP2D6 *2/*4/*5 Poor Metabolizer)

Consider alternative drug or consider a 50% reduction of imipramine recommended starting dose and then titrate in response to imipramine and desipramine plasma concentrations. Available alternative drugs not sensitive to CYP2D6 function include: sertraline, citalopram, escitalopram and fluvoxamine.

Lorazepam (Ativan)

Possible Altered Response to Lorazepam (UGT2B15 *2/*2 Poor Metabolizer)

Lorazepam clearance is reduced in this patient. However, there is insufficient evidence as to whether this change results in a significant clinical effect. Consider monitoring the patient for increased sedation and adjust dosing accordingly.

Metoprolol (Lopressor)

Significantly Increased Sensitivity to Metoprolol (CYP2D6 *2/*4/*5 Poor Metabolizer)

Heart Failure: Consider alternative beta-blockers such as bisoprolol or carvedilol or prescribe metoprolol at a lower dose. When compared to a normal metabolizer, a poor metabolizer may require 75% dose reduction. Other indications: Consider alternative beta-blockers such as bisoprolol or atenolol or prescribe metoprolol at a lower dose. When compared to a normal metabolizer, a poor metabolizer may require 75% dose reduction. If metoprolol is prescribed, be alert to adverse events (e.g. bradycardia, cold extremities).

Mexiletine (Mexitil)

Significantly Increased Sensitivity to Mexiletine (CYP2D6 *2/*4/*5 Poor Metabolizer)

Consider prescribing a lower mexiletine dose. A slow titration with ECG recording and monitoring of mexiletine plasma concentrations are recommended until a favorable clinical response is achieved.

Morphine (MS Contin)

Altered Response to Morphine (COMT Val158Met GG Homozygous Wild-Type)

The patient may require higher doses of morphine for adequate pain control. Dosing regimen needs to be individualized for each patient, taking into account the patient's prior analgesic treatment experience. Monitor the patient closely for respiratory depression, especially within the first 24-72 hours of initiating therapy.

Naltrexone (Vivitrol)

Altered Response to Naltrexone (OPRM1 A118G AA Normal OPRM1 Function)

Treatment of alcohol dependence: the patient's has the wild-type genotype for OPRM1 that is associated with a poorer outcome with naltrexone therapy. Naltrexone-treated patients not carrying the 118A> G mutation, are less likely to respond to this drug and may have higher relapse rates than those who are carriers of this mutation.

Nortriptyline (Pamelor)

Increased Sensitivity to Nortriptyline (CYP2D6 *2/*4/*5 Poor Metabolizer)

Select an alternative drug or consider prescribing nortriptyline at a reduced dose (50% reduction) with monitoring of plasma concentrations of nortriptyline and metabolites. Available alternative drugs not sensitive to CYP2D6 function include: sertraline, citalopram, escitalopram and fluvoxamine.

Olanzapine (Zyprexa)

Non-Response to Olanzapine (CYP1A2 *1F/*1F Normal Metabolizer - Higher Inducibility)

There is little evidence regarding the impact of CYP1A2 genetic variants on olanzapine response. Smokers may be at risk for non-response at standard doses. Careful monitoring is recommended during dosing adjustment. Smoking cessation may increase plasma drug levels leading to adverse events and therapeutic drug monitoring accompanied by dose reduction may be needed in patients who have quit smoking.



Oxazepam (Serax)

Possible Altered Response to Oxazepam (UGT2B15 *2/*2 Poor Metabolizer)

Oxazepam clearance is reduced in this patient. However, there is insufficient evidence as to whether this change results in a significant clinical effect. Consider monitoring the patient for increased sedation and adjust dosing accordingly.



Paroxetine (Paxil)

Possible Sensitivity to Paroxetine (CYP2D6 *2/*4/*5 Poor Metabolizer)

At standard label-recommended dosage, paroxetine levels are expected to be high. Careful titration is recommended until a favorable response is achieved. When compared to a CYP2D6 normal metabolizer, a poor metabolizer may require a 50% dose reduction.



Perphenazine (Trilafon)

Increased Sensitivity to Perphenazine (CYP2D6 *2/*4/*5 Poor Metabolizer)

Patients with a decreased CYP2D6 function will eliminate perphenazine more slowly which can result in higher drug concentrations and possibly higher adverse events (extrapyramidal symptoms). Consider close monitoring and dose reduction to avoid toxicity.



Pimozide (Orap)

Increased Sensitivity to Pimozide (CYP2D6 *2/*4/*5 Poor Metabolizer)

In CYP2D6 poor metabolizers, pimozide doses should not exceed 4 mg/day in adults or 0.05 mg/kg/day in children, and doses should not be increased earlier than 14 days.



Propafenone (Rythmol)

Increased Sensitivity to Propafenone (CYP2D6 *2/*4/*5 Poor Metabolizer)

Consider reducing the propafenone dose and monitor ECG. Compared to normal metabolizers, poor metabolizers may require a 70% dose reduction. Consider monitoring for plasma concentrations.



Risperidone (Risperdal)

Significantly Increased Sensitivity to Risperidone (CYP2D6 *2/*4/*5 Poor Metabolizer)

Consider alternative drug; available alternative drugs include: quetiapine, olanzapine, clozapine. Or, prescribe risperidone at a reduced dose and be extra alert of adverse events and adjust dosage in response to clinical response and tolerability.



Sertraline (Zoloft)

Moderate Sensitivity to Sertraline (CYP2C19 *2/*17 Provisional Intermediate Metabolizer)

Sertraline should be used with caution in patients with reduced CYP2C19 activity. Because there is insufficient data to allow calculation of dose adjustment when sertraline is prescribed, consider using a lower than recommended dose and be alert to adverse drug events such as nausea, vomiting or diarrhea.



Tacrolimus (Prograf)

Hyporesponder to Tacrolimus (CYP3A5 *1/*3 Intermediate Metabolizer)

Studies have shown patients with a this genotype may be at increased risk for acute transplant rejection while taking a standard dose of tacrolimus. Therefore a tacrolimus dose increase with close monitoring are strongly recommended to achieve therapeutic effect.



Tamsulosin (Flomax)

Increased Sensitivity to Tamsulosin (CYP2D6 *2/*4/*5 Poor Metabolizer)

Tamsulosin is metabolized at a slower rate in CYP2D6 poor metabolizers; this results in significantly higher serum concentrations of tamsulosin. Therefore, this drug should be used with caution in patients known to be CYP2D6 poor metabolizers, particularly at a daily dose higher than 0.4 mg.



Tetrabenazine (Xenazine)

Increased Sensitivity to Tetrabenazine (CYP2D6 *2/*4/*5 Poor Metabolizer)

Individualization of dose with careful weekly titration is required. The first week's starting dose is 12.5 mg daily; second week, 25 mg (12.5 mg twice daily); then slowly titrate at weekly intervals by 12.5 mg to a tolerated dose. **The maximum daily dose in CYP2D6 poor metabolizers is 50 mg with a maximum single dose of 25 mg.** If serious adverse events occur, titration should be stopped and the dose of tetrabenazine should be reduced. If the adverse event(s) do not resolve, consider withdrawal of tetrabenazine.

Thioridazine (Mellaril)

Increased Sensitivity to Thioridazine (CYP2D6 *2/*4/*5 Poor Metabolizer)

Reduced cytochrome CYP2D6 activity results in elevated plasma levels of thioridazine and would be expected to augment the prolongation of the QTc interval associated with thioridazine and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as Torsades de pointes type arrhythmias. Such an increased risk may result also from the additive effect of coadministering thioridazine with other agents that prolong the QTc interval. Therefore, thioridazine is contraindicated in patients with reduced levels of CYP2D6 activity.

Timolol (Timoptic)

Increased Sensitivity to Timolol (CYP2D6 *2/*4/*5 Poor Metabolizer)

Potentiated systemic beta-blockade (e.g., bradycardia) has been reported during timolol treatment by patients with decreased CYP2D6 activity. Monitor patient for treatment-related adverse effects.

Tizanidine (Zanaflex)

Possible Non-Response to Tizanidine (CYP1A2 *1F/*1F Normal Metabolizer - Higher Inducibility)

There is little evidence regarding the impact of CYP1A2 genetic variants on tizanidine response. Smokers may be at risk for non-response and may require higher doses. There is an association between high tizanidine plasma concentrations and the risk of hypotension and excessive sedation, therefore careful monitoring is recommended during dosing adjustment. Smoking cessation may increase plasma drug levels leading to excessive hypotension and sedation. Careful monitoring accompanied by dose reduction may be needed in patients who have quit smoking.

Tolterodine (Detrol)

Possible Sensitivity to Tolterodine (CYP2D6 *2/*4/*5 Poor Metabolizer)

Tolterodine is metabolized at a slower rate in CYP2D6 poor metabolizers; this results in significantly higher serum concentrations of tolterodine and in negligible concentrations of its active metabolite (5-hydroxymethyltolterodine). Considering the antimuscarinic potency of tolterodine and its active metabolite and the protein binding of these compounds, tolterodine accounts for the major part of the clinical effect in poor metabolizers and the same dosage can be applied irrespective of phenotype status.

Patients with Congenital or Acquired QT Prolongation: The effect of tolterodine on the QT interval prolongation is greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day and is more pronounced in CYP2D6 poor metabolizers than normal metabolizers. This should be considered when tolterodine is prescribed to patients with a known history of QT prolongation or patients who are taking Class IA or Class III antiarrhythmics.

Tramadol (Ultram)

Non-Response to Tramadol (CYP2D6 *2/*4/*5 Poor Metabolizer)

Avoid prescribing tramadol and consider alternative opioids other than codeine or consider a non-opioid analgesic such as a NSAID or a COX-2 inhibitor. Unless contraindicated, available alternative opioids (not sensitive to CYP2D6 function) include: Fentanyl, Morphine, Hydromorphone, Oxycodone, Tapentadol and Meperidine.

Trimipramine (Surmontil)

Increased Sensitivity to Trimipramine (CYP2D6 *2/*4/*5 Poor Metabolizer)

Consider alternative drug or consider a 50% reduction of trimipramine recommended starting dose and then titrate in response to trimipramine plasma concentrations. Available alternative drugs not sensitive to CYP2D6 function include: sertraline, citalopram, escitalopram and fluvoxamine.

Venlafaxine (Effexor)

Significantly Increased Sensitivity to Venlafaxine (CYP2D6 *2/*4/*5 Poor Metabolizer)

Consider alternative drug; available alternative drugs include: citalopram and sertraline. Or, prescribe venlafaxine and be extra alert of adverse events and adjust dosage in response to clinical response and tolerability. Monitor O-desmethylvenlafaxine plasma concentrations.



Prescription Alert

DOB

This individual has been tested for gene variants that may affect medications prescribed.

GENE	ANKK1	Altered DRD2 function	RESULT
	COMT	High COMT Activity	
	CYP1A2	Normal Metabolizer - Higher Inducibility	
	CYP2B6	Normal Metabolizer	
	CYP2C19	Intermediate Metabolizer	
	CYP2C9	Normal Metabolizer	
	CYP2D6	Poor Metabolizer	
	CYP3A4	Normal Metabolizer	
	CYP3A5	Intermediate Metabolizer	
	OPRM1	Normal OPRM1 Function	
	SLCO1B1	Normal Transporter Function	
	UGT2B15	Poor Metabolizer	
	VKORC1	Low Warfarin Sensitivity	

Healthcare Providers: For up-to-date information concerning the impact of these genetic tests on drug prescribing by may consult the PharmGKB database:

www.pharmgkb.org

Note: This patient has also been tested for common variants in the Factor II, Factor V, MTHFR, and ApoE genes. These results are available on the patient's medical records.